CANDIDATE SUBSTANCES FOR SPACE BIOPROCESSING METHODOLOGY AND DATA SPECIFICATION FOR BENEFIT EVALUATION

TASK ORDER V FINAL REPORT

Econ INCORPORATED

77-265-1

NINE HUNDRED STATE ROAD
PRINCETON, NEW JERSEY 08540
609 924-8778

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CONTRACT NASW-3047

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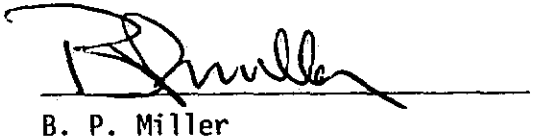
January 13, 1978

NOTE OF TRANSMITTAL

This study of the methodology and data requirements for the benefit evaluation of candidate substances for space bioprocessing was performed by ECON, Incorporated for the Office of Applications, National Aeronautics and Space Administration. The work was performed as Task V, Contract NASW-3047. This study is the first phase of a three-phase program that is intended to apply economic evaluation and analytical techniques to the decision problems faced by the NASA space bioprocessing program.

A primary objective of this first phase, described in this report, is to recommend the appropriate evaluation techniques necessary to obtain measures of the potential economic benefits which may occur as a result of the successful completion of various space bioprocessing endeavors. In addition, this first phase considers the feasibility of performing economic evaluation for a specific set of candidate substances, and examines the data needs for the subsequent evaluation of each of these substances. In two subsequent phases it is proposed to collect the specified data and evaluate the benefits of each candidate substance, and to perform a decision analysis that could be used to evaluate the probable economic outcome of each of the proposed projects.

The project team for this study at ECON consisted of Ms. Celia Drumheller, Mr. Keith Lietzke and Mr. B.P. Miller. The candidate substances examined in this study were suggested by the NASA Technical Officer, Dr. James Bredt.



B. P. Miller
Vice President

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SUMMARY

SUMMARY

The results of this study show that analytical and quantitative economic techniques are broadly applicable to the evaluation of the economic benefits of a wide range of candidate substances for space bioprocessing.

Two previous studies of candidate substances for space bioprocessing have provided preliminary benefit estimates for three substances: namely, separation and classification of lymphocyte subgroups, separation of urokinase producing cells, and separation of beta cells for treatment of diabetes.[1,2]

On the basis of expected clinical applications, as well as the size of the patient population that could be affected by the clinical applications, the eight substances listed on the opposite chart, are recommended for further benefit evaluation. These studies indicate that a transitional probability methodology can be used to model at least one clinical application for each of these substances. In each recommended case, the disease and its therapy are sufficiently well understood and documented, and the statistical data is available to operate the model and produce estimates of the impact of new therapy systems on the cost of treatment, morbidity and mortality. Utilizing the morbidity and mortality information produced by the model, a standard economic technique called the Value of Human Capital can be used to estimate the social welfare benefits that could be attributable to the new therapy systems.

[1] Preliminary Benefit Analysis of Biological Space Processing, ECON, Inc., September 1976.

[2] Benefit Evaluation of Space Processing of Biological Materials. Contract NAS-9-15378, Final Report (in preparation).

SUMMARY

- QUANTITATIVE BENEFITS OF SPACE BIOPROCESSING CAN BE ESTIMATED FOR SPECIFIC DISEASE TREATMENTS

- TRANSITIONAL PROBABILITY AND VALUE OF HUMAN CAPITAL METHODOLOGIES ARE BROADLY APPLICABLE

- RECOMMENDED FOR FURTHER BENEFIT STUDY
  - + PEPTIDE HORMONES
  - + LYMPHOCYTES
  - + GRANULOCYTES
  - + STEM CELLS
  - + PLASMA CELLS
  - + MEGAKARYOCYTES
  - + UROKINASE
  - + BETA CELLS

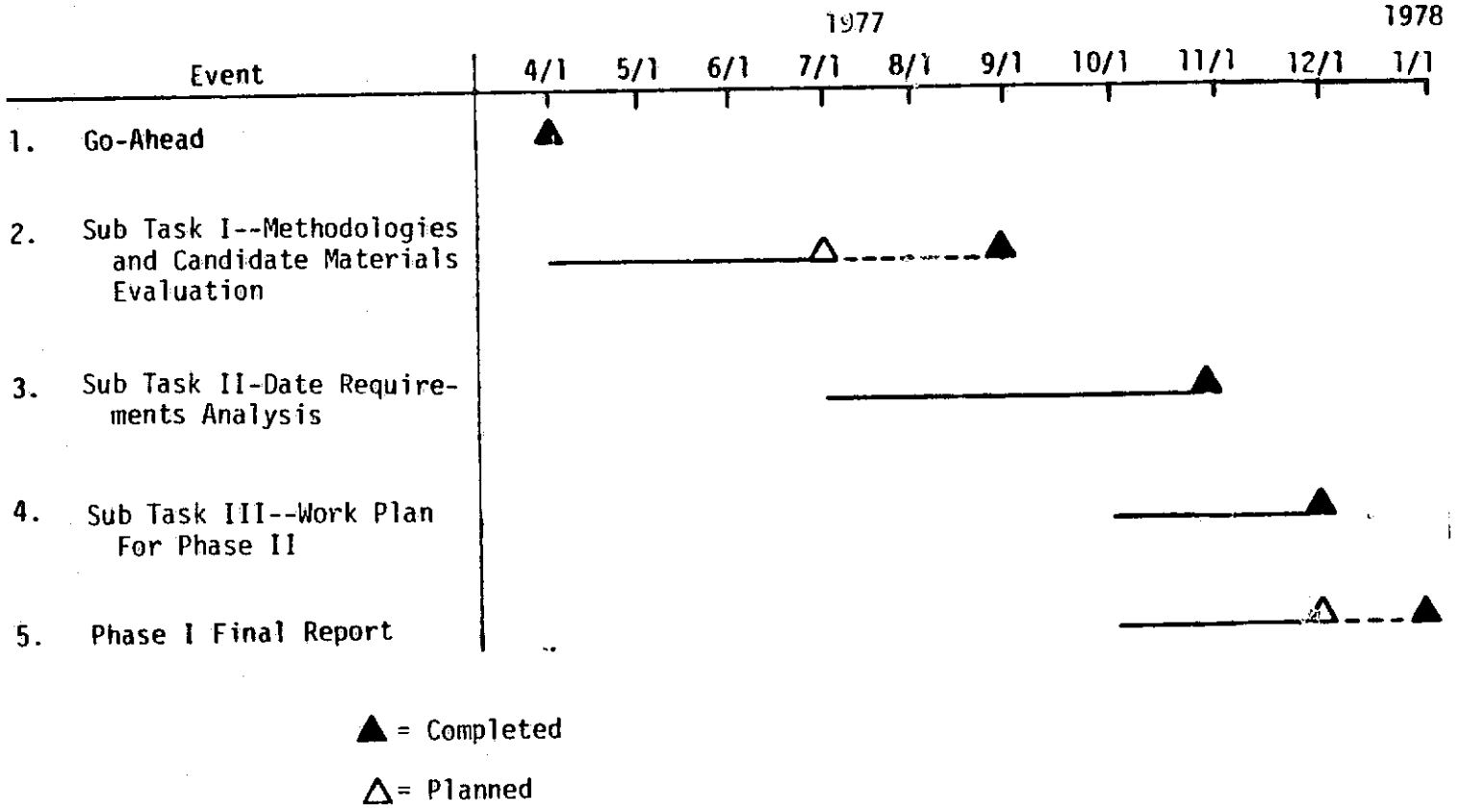
INTRODUCTION

MILESTONE SCHEDULE FOR PHASE I

The schedule of the work performed during this phase is shown on the opposite chart. The study began with a suggested set of candidate substances for space bioprocessing. The common denominator for the processing to be performed on these substances in space is electrophoretic separation.

Currently utilized techniques for medical research benefit evaluation were surveyed in Subtask I. Clinical applications were then identified for each of the candidate substances. For each substance and clinical application, the current form of treatment and the new form of treatment using the candidate substance were identified. For each clinical application, both present and proposed, statistical data sources were examined for the availability of data on the incidence of the disease, and the cost and duration of stages of treatment. These same sources were examined for the availability of data on morbidity and mortality. Based upon this information, a model of the disease, its present treatment and the new treatment possibilities afforded by the candidate substance, was prepared and reviewed with medical experts. Thus, the major output of this study is a model, and the specification of the data needs and sources for the operation of the model, that could be used for the evaluation of the benefits for each candidate substance.

MILESTONE SCHEDULE FOR SPACE BIOPROCESSING - PHASE I



DEFINITION OF ECONOMIC AND SOCIAL BENEFITS

Two classes of benefits must be considered when the benefits of a proposed new method of disease treatment are to be evaluated. For the purpose of this study, these two classes of benefits are considered to be the economic benefits and social benefits. The economic benefits are defined as those benefits that occur in the private and public sector from the changes in the cost of treatment of the disease. Social benefits are defined as those benefits that result from decreases in mortality and/or morbidity as a result of the new treatment process. For example, prior to the use of penicillin, mary bacterial infections required hospitilization and long periods of convalescence. With the use of penicillin, an economic benefit results as the cost of treatment of bacterial infection has been decreased. Further, a social benefit also results as the use of penicillin has reduced the incidence of death and periods of disability from bacterial infection.

The purpose of a benefit evaluation study is to express these benefits in measurable quantities such as dollars and years of productive life extension.

The benefits of the space research with the biological materials can be calculated as the differences between the cost and life expectancy associated with existing treatment systems, and the similar characteristics associated with new treatment systems resulting from the processing of biological materials in space.

ECONOMIC AND SOCIAL BENEFITS

- TWO BENEFIT COMPONENTS
  - + ECONOMIC - COST OF DISEASE TREATMENT
  - + SOCIAL - DECREASED MORTALITY, MORBIDITY AND/OR INCREASED PRODUCTIVITY
- OBJECTIVE IS TO CONVERT ABOVE TO SCALAR QUANTITIES
  - + DOLLARS
  - + YEARS OF PRODUCTIVE LIFE EXTENSION

TECHNIQUES FOR ESTIMATING BENEFITS OF BIOMEDICAL RESEARCH

Many different numerical techniques have been used to estimate the economic and social benefits of biomedical research. The most widely used techniques include the value of human capital (or life-table statistics), Monte Carlo simulations, and transitional probability methods.

First-cut estimates of benefits within disease categories are often calculated from life-table statistics. Assumptions are made on the effects that research gains would have on mortality rates, whereupon the expected gains in longevity can be computed. These are directly translatable into life years preserved or, by valuing productivity according to the human capital model, into saved productivity. Adjustments for quality-of-life may also be made.[1] This approach was pioneered by Rice.[2] Extensions of the value of human capital approach can take into account demographic characteristics, personal habits or risk factors.

The concept of using Monte Carlo simulation is attractive; however, its use has been limited by data availability and the sophistication of the modeling required. The attractiveness of this approach results from the fact that diseases are randomly contracted, intervention is possible after a variable amount of time, and stochastic processes influence diagnoses and intermediate and final outcomes. Since the assumed or observed statistical patterns are often idiosyncratic, precise analytic treatment of them may be impossible. Such Monte Carlo simulation of heart disease[3] has enabled evaluation of alternative treatment strategies. The novelty of Monte Carlo estimations in health and the large number of assumptions on which they are predicated has to date limited their influence on policy.

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[1] As in Preston, S.H., et al., 1972, Causes of Death: Life Table for National Populations, Seminar Press, New York.

[2] Rice, D. P., 1966, Estimating the Cost of Illness, PHS Publication 947-6, U.S. Government Printing Office, Washington, D.C.

[3] Acton, J. P., in Epidemiologic Methods, Little Brown, Boston (1970); and Cretin, S., 1974, A Model of the Risk of Death From Myocardial Infarction, Technical Report No. 0974, M.I.T. Operations Research Center, Cambridge, Massachusetts.

TECHNIQUES FOR ESTIMATING BENEFITS OF BIOMEDICAL RESEARCH

- VALUE OF HUMAN CAPITAL--(LIFE TABLE STATISTICS)
  - + ESTIMATE EFFECTS OF RESEARCH ON MORTALITY
  - + CAN BE ADJUSTED FOR DISABILITY AND DISCOMFORT (QUALITY-ADJUSTED LIFE YEARS)
  - + CAN BE DIFFERENTIATED BY DEMOGRAPHIC CHARACTERISTICS, AGE, NUTRITION, PERSONALITY, PREVIOUS MEDICAL HISTORY, OR OTHER FACTORS
  - + WIDELY USED BY ANALYSTS FOR AILMENTS THAT LEAD TO AN INVARIENT SERIES OF EVENTS
- MONTE CARLO SIMULATION
  - + $N^{\underline{th}}$ EVENT CAN BE DEPENDENT UPON PRIOR EVENTS
  - + MOST FLEXIBLE BUT MOST COSTLY METHOD OF MODELING
  - + VERY LIMITED USE--MORE DIFFICULT TO SOLVE

Transitional probability, or Markov chain methods, are appropriate when the following four conditions can be met in modeling the disease:

1. A finite number of discrete, well-defined states exist
2. A set interval best explains the transition timing
3. The transition probabilities depend only upon the current state and not on history
4. The transition probabilities are stationary over time.

Transitional probability (Markovian) methods are receiving increased attention and application in health. Laboratory[1] and behavioral research[2] has successfully used these tools to explain observed phenomena. Among diseases, kidney failure--with its many possible states of patient stabilization--has been most extensively analyzed according to transitional probability tools.[3] Cardiac arrhythmias have been investigated and explained as Markov phenomena, leading to improvements in diagnosis.[4] Bush[5] laid out a general Markovian methodology for analyzing patient outcomes, taking tuberculosis as an illustrative case.

Cretin[6] showed that the treatment and survival of patients suffering myocardial infarction could be efficiently analyzed using a semi-Markovian model of state transitions. A related semi-Markovian model was displayed by Weiss and Zelen.[7] Their model avoided the Markovian assumptions of set transition times and enabled a more general family of transition functions to be dealt with. With this methodology they explained leukemic recessions although goodness-of-fit criteria were not applied. Silver[8] analyzed venereal disease according to semi-Markovian analysis and showed how the requisite computations might be facilitated.

[1] Boyarsky, A., and P. B. Noble, 1977, A Markov Chain Characterization of Human Neutrophil Locomotion Under Neutral and Chemotactic Conditions, Canadian Journal of Physiological Pharmacology, 55(1):1-6; and S. M. Rudolfer and H. U. May, 1975, On the Markov Properties of Interspike Times in the Cat Optic Tract, Biological Cybernetic, 19(4):197-199.

[2] Natale, M., 1976, A Markovian Model of Adult Gaze Behavior, J. Psycholinguist Res., 5(1):53-63; and W. A. Thompson and I. Vertinsky, 1975, Application of Markov Chains: to Analysis of a Simulation of Birds' Foraging, Journal of Theoretical Biology, 53(2):285-306.

[3] Urakable, S., et al., 1976, Kidney Function Tests and Prognosis--Application of Markov Chains, Japanese Journal of Clinical Medicine, 34(9):2864-2869; K. Cooper and C. Blagg, 1973, Modified Markov Chain Analysis in Long Term Planning of Treatment Programs for Chronic Renal Failure, Proc. Clinical Dialysis Transplant Forum, 3:162-169; and S. Urakable, et al., 1975, Prognosis of Chronic Glomerulonephritis in Adult Patients Estimated on the Basis of the Markov Process, Clinical Nephrology, 3(2):48-53.

[4] Gersch, W., et al., 1975, PVC Detection by the Heart-Beat Interval Data--Markov Chain Approach, Computers and Biomedical Research, 8(4):370-378.

[5] Bush, J. W., et al., 1971, Estimating Health Program Outcomes Using a Markov Equilibrium Analysis of Disease Development, American Journal of Public Health, 61(12):2362-2374.

[6] Op. cit.

[7] Weiss, G. H. and M. Zelen, 1965, A Semi-Markov Model for Clinical Trials, Journal of Applied Problems, 2:269-285.

[8] Silver, E. A., 1968, A Model of the Incidence of Veneral Disease in a Population of Associated Individuals, from Record of the IEEE Systems Science and Cybernetics Conference, October 1968, Catalog No. 68 C 23-SSC.

TECHNIQUES FOR ESTIMATING BENEFITS OF BIOMEDICAL RESEARCH (CONTINUED)

- TRANSITIONAL PROBABILITY METHODS
  - + WORK BEST WHEN DISEASE AND INTERVENTION CONSIST OF A FINITE NUMBER OF DISCRETE STATES
  - + RESEARCH IS PRESUMED TO ACT BY ALTERING PROBABILITY OF TRANSITIONING FROM STATE TO STATE
  - + TRANSITION PROBABILITIES MUST DEPEND ONLY ON THE CURRENT STATE--NOT ON HISTORY
  - + TRANSITION PROBABILITIES ARE STATIONARY WITH TIME
  - + HAS BEEN USED TO MODEL KIDNEY FAILURE, MYOCARDIAL INFARCTION, LEUKEMIC RECESSIONS, VENEREAL DISEASE, GERIATRIC POLICIES AND PATIENT MANAGEMENT
  - + WIDELY ACCEPTED BY ANALYSTS AND TAUGHT IN COURSES IN PUBLIC DECISION MAKING

END STAGE RENAL DISEASE: AN EXAMPLE OF A TRANSITIONAL PROBABILITY MODEL

In a quantitative approach to human disease process analysis it is common to speak of the "states" that a patient may occupy. In a very simple example, the states could be "healthy" and "sick." In a more detailed breakdown, the states of treatment or complications for a given disease and therapy could be specified.

The opposite chart shows the transitional probability model for End Stage Renal Disease (ESRD) developed in an earlier study.[1] The known treatments for this disease today are dialysis and kidney transplantation. In this case, it is believed that lymphocyte subgroup separation in space will bring about a better understanding of the human immunological system, resulting in better donor and recipient matching, and thus a better success rate in kidney transplantation. The five states circled by the dashed line are the possible states reached after contraction of ESRD. These five states were used in the model, thus ignoring healthy people and people who have kidney disease but not ESRD. A discrete Markov process is then defined for these five states, dictating that, each year for a given patient, a transition would occur. It should be noted that in some cases the transition could result in movement from one state to another, and in cases, the transition could result in a patient remaining in a given state. Statistics were then collected to enable the extension of the economic and social benefits for three cases: (1) current state-of-the-art, (2) partial improvement due to space processing; and (3) optimistic improvement due to space processing. The statistics collected for each state were:

1. How long did the patient live after contracting ESRD?

2. How many years after contracting ESRD did the patient enter each state?

3. How many years did the patient reside in each state?

4. What was the cost to the public sector?

5. What was the cost to the private sector?

The treatment possibilities for each of the three cases were estimated through consultation with experts in kidney disease and kidney transplants, and from available statistical sources. The model was then operated and benefit estimates obtained for the two improvement cases relative to the present state-of-the-art treatment of ESRD.

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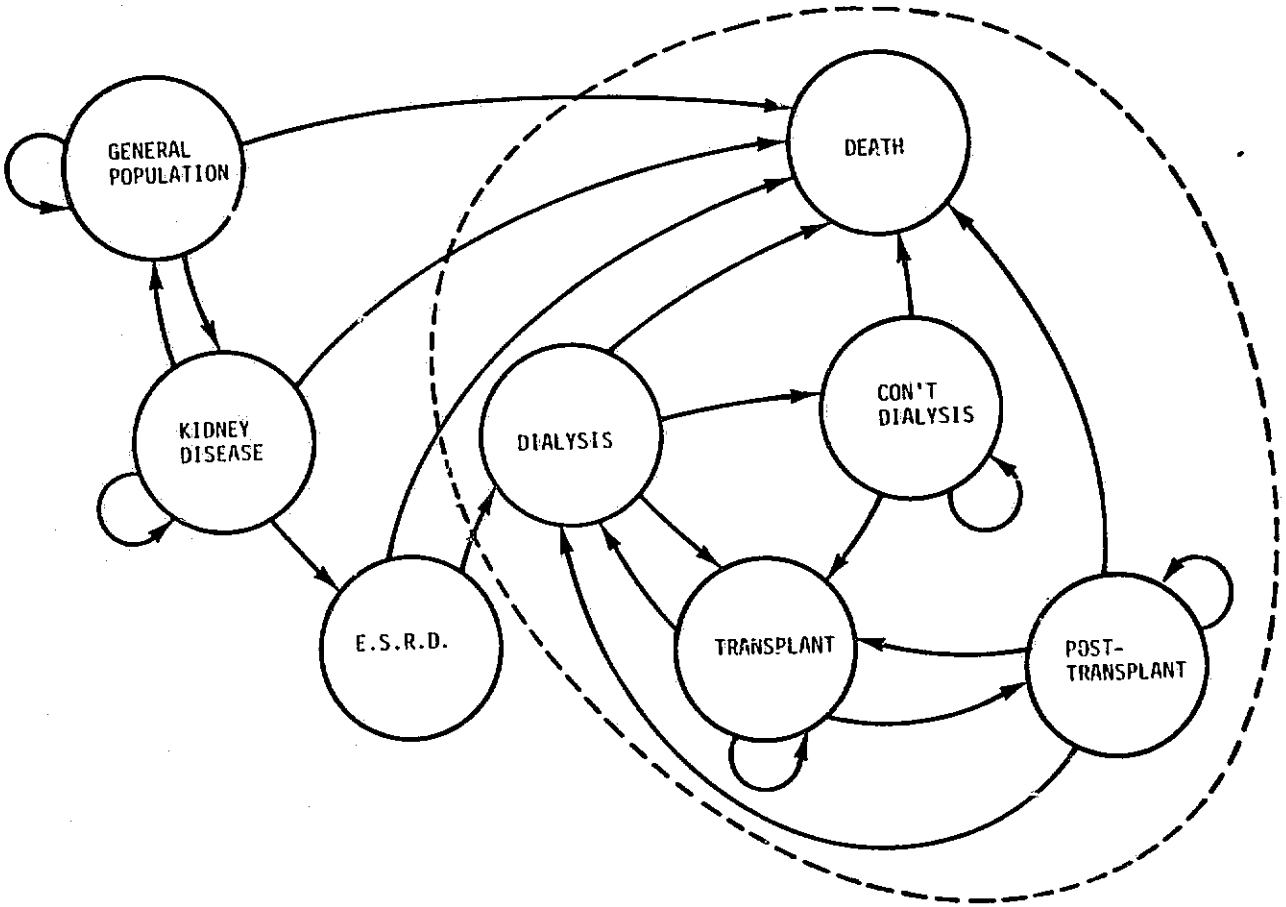
[1] An Evaluation of the Economic Benefits of Processing Biological Materials in Space, B. P. Miller, Paper 77-59. 28th Congress of the International Astronautical Federation.

END STAGE RENAL DISEASE MODEL: AN EXAMPLE OF A TRANSITIONAL PROBABILITY MODEL



PRESENT VALUE OF HUMAN CAPITAL (1976)

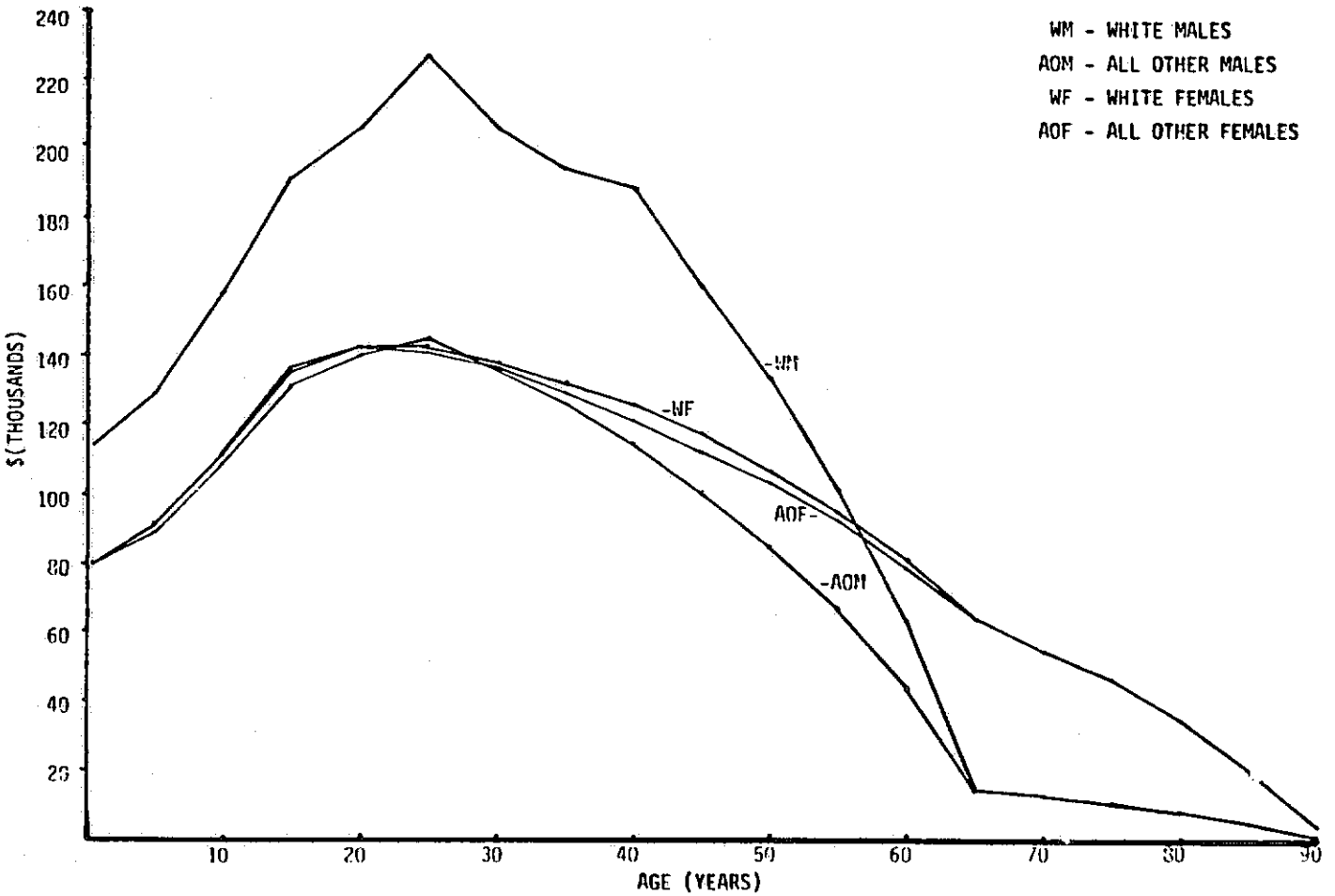
Typical human capital curves such as those opposite were developed over a decade ago by Dorothy P. Rice. The value obtained from these curves for any particular year of an average person's life represents the discounted value. Thus, if that sum were invested in an interest-bearing savings account, withdrawals equal to the average salary could be made for the years which the deceased would have lived. The total money thus withdrawn from the account would yield far more than the amount deposited (the amount of the value at the age on the curve).

This particular curve was developed by ECON using a modified Rice technique.[1] Mean earnings of full-time, year-round employees were obtained from the U.S. Department of Labor. The earning figures were weighted by the percentage of the work force falling in that category (i.e., white male, all other female, etc.) and adjusted upward to account for wage supplements such as employer contributions for social insurance, private pension and welfare funds. Housekeeping services were valued at 70 percent of $4000 per year for women and $400 for men under 65 years, and $4000 for retired females and $1000 per year for retired males.

A 6 percent discount rate was used.

[1] Cooper, Barbara S. and Rice, Dorothy P. The Economic Cost of Illness Revisited. Social Security Administration, Office of Research and Statistics. 1975

PRESENT VALUE OF HUMAN CAPITAL ($1976)

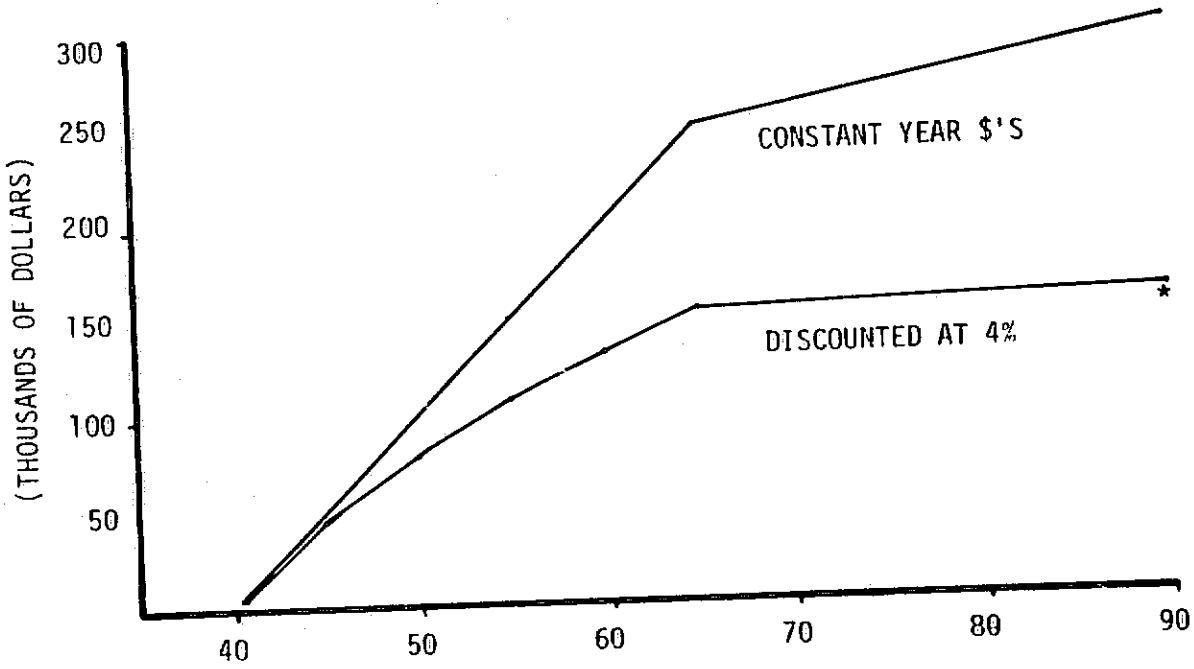


CUMULATIVE LIFE EARNINGS

In order to better understand the present value of human capital, this simplified example is provided. The example assumes a white male, aged 40, is earning $10,000 per year (for simplicity sake) until age 65 and then his value would be $1000 per year for assistance provided in the home. We assume here that he dies at age 40 and we wish to estimate his potential future earnings if he had not died. The cumulative and the discounted value of those earnings is shown. The discounted value assumes a 4 percent discount rate and the earnings are discounted back to age 40. The cumulative discounted value at the end of the curve (age 90) would then be one entry in preparing a present-value-of-human-capital curve for this individual. If this process is repeated at each age, a curve similar to that shown on page 17 can be drawn.

CUMULATIVE LIFE EARNINGS

ASSUMED: WHITE MALE, AGED 40, INCOME $10,000/YR
UNTIL AGE 65, THEN $1000/YR (HOUSEKEEPING VALUE)



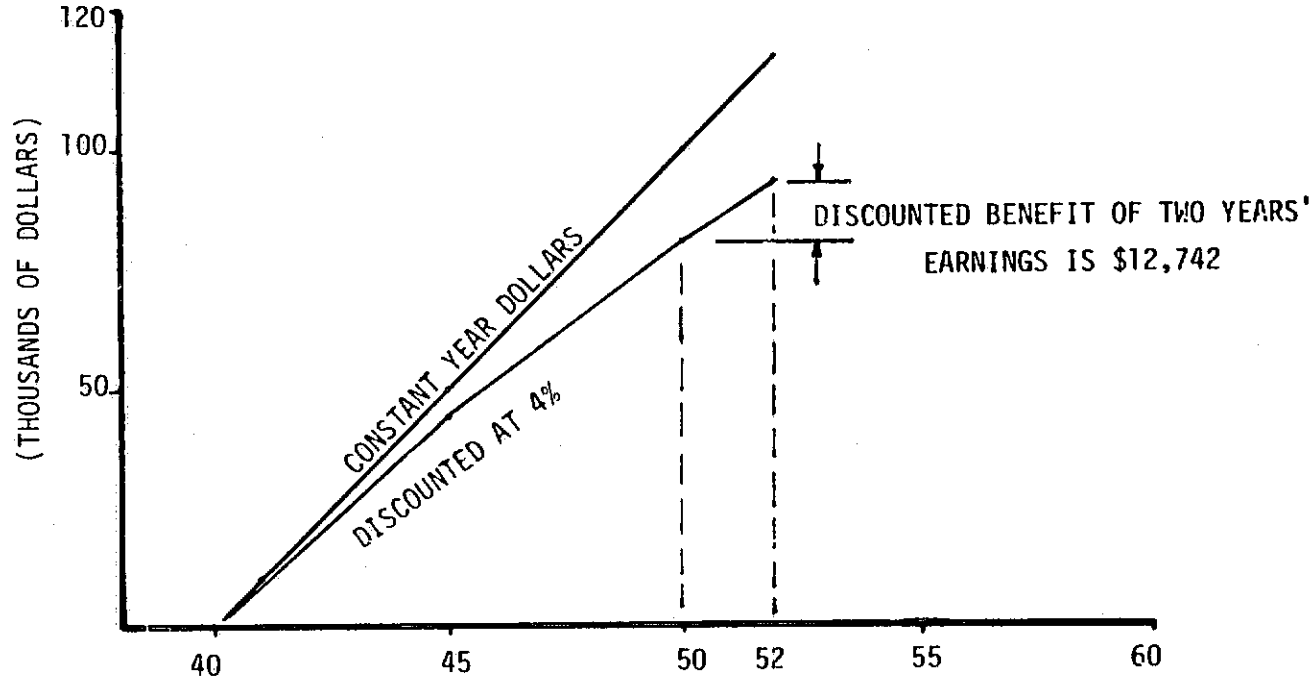
*THIS VALUE REPRESENTS THE ENTRY (IN THIS EXAMPLE) FOR THIS CLASS OF INDIVIDUAL IN A PRESENT-VALUE-OF-HUMAN-CAPITAL CURVE

EXAMPLE OF THE BENEFIT OF EXTENDING LIFE FOR 2 YEARS

The previous figure illustrated the technique utilized to determine the present value of human capital out to age 90. Now let us take an example that is pertinent to the case at hand, namely, the benefit of postponing death for N years. Here we have the same white male earning $10,000 per year becoming afflicted with a disease at age 40. In this example, with the present treatment, his average life expectancy is 10 years, but with the new treatment his life expectancy is increased to 12 years. Thus, we wish to know the benefit of his life for the two additional years (12 years' earnings minus 10 years' earnings) and discounting constant year dollars back to age 40 (11 and 12 years, respectively) we see the value is $12,742 dollars. This technique is suggested as an appropriate method for estimating the value of the social benefit resulting from life extension.

EXAMPLE OF THE BENEFIT OF EXTENDING LIFE FOR 2 YEARS

DISEASE ONSET ASSUMED AT AGE 40,
DISCOUNT RATE OF 4%



EVALUATION OF CANDIDATE SUBSTANCES

GENERAL CONSIDERATIONS FOR ECONOMIC ANALYSIS

There are certain general aspects of any new bioprocessing of substances which must be considered in order to properly evaluate possible decision alternatives. Some of these are briefly outlined here. Those factors that are considered during this phase are used to assess the feasibility of applying current economic benefit-estimating techniques and provide some insight to the order of magnitude of benefits expected. Those factors not considered are not of lesser importance, but are outside of the scope of this first phase. However, each of the factors listed does have a place in the decision-making process.

The following comments are appropriate to those factors not considered. "Technical difficulties" refers to the difficulties and likelihood of success of the separation process. "Medical difficulties" refers to any problems which may arise after a successful separation prior to actual clinical application. The "length of time to benefit realization" depends on the length of time required to develop and approve the treatments and to disease-specific delays between treatment and benefit realization.

GENERAL CONSIDERATIONS FOR ECONOMIC ANALYSIS

CONSIDERED IN THIS PHASE

+ CLINICAL APPLICATIONS
+ DATA AVAILABILITY
+ EXPECTED MAGNITUDE OF INDIVIDUAL INDIVIDUAL BENEFITS
+ POTENTIAL PATIENT POPULATION
+ MODELING

NOT CONSIDERED IN THIS PHASE

+ SCIENTIFIC WORTH
+ TECHNICAL DIFFICULTIES
+ MEDICAL DIFFICULTIES
+ LENGTH OF TIME TO BENEFIT REALIZATION

SUBSTANCES STUDIED FOR POSSIBLE SPACE BIOPROCESSING

The substances studied for space processing were considered first on the basis of the existence of a known clinical application. In order to estimate benefits, it is necessary that a clinical application be identified. Those substances recommended for further study were found to have at least one reasonably well understood clinical application. Those substances which were not found to have known applications or where such possible uses were not clearly understood are not recommended for further benefit study at this time. It should be noted that this selection process applies only to further benefit studies, and does not imply that research should not be continued on those substances not recommended for further benefit study at this time.

SUBSTANCES STUDIED FOR POSSIBLE SPACE BIOPROCESSING

RECOMMENDED FOR FURTHER BENEFIT STUDY ON THE BASIS OF CLINICAL APPLICATIONS ONLY

+ β CELLS OF THE ISLETS OF LANGERHANS
+ HUMAN GROWTH HORMONE (HGH) PRODUCING CELLS
+ PEPTIDE HORMONES
+ LYMPHOCYTES
+ GRANULOCYTES
+ STEM CELLS
+ PLASMA CELLS
+ MEGAKARYOCYTES

NOT RECOMMENDED FOR FURTHER BENEFIT STUDY ON THE BASIS OF CLINICAL APPLICATION ONLY

+ MONOCYTES
+ MACROPHAGES
+ SYNTROPHOBLASTS
+ ENDOTHELIAL CELLS
+ NERVE CELL AXIONS
+ SEA URCHIN EGGS

BETA CELLS ISLETS OF LANGERHANS

The separation of the Beta Cells of the Islets of Langerhans found in the human pancreas by electrophoresis in space could possibly lead to the culturing of these cells for the production of human insulin or to the culturing of these cells for direct transplantation in patients. Either use would serve as a new treatment of the patient with insulin-dependent diabetes mellitus.

BETA CELLS ISLETS OF LANGERHANS

CLINICAL APPLICATION

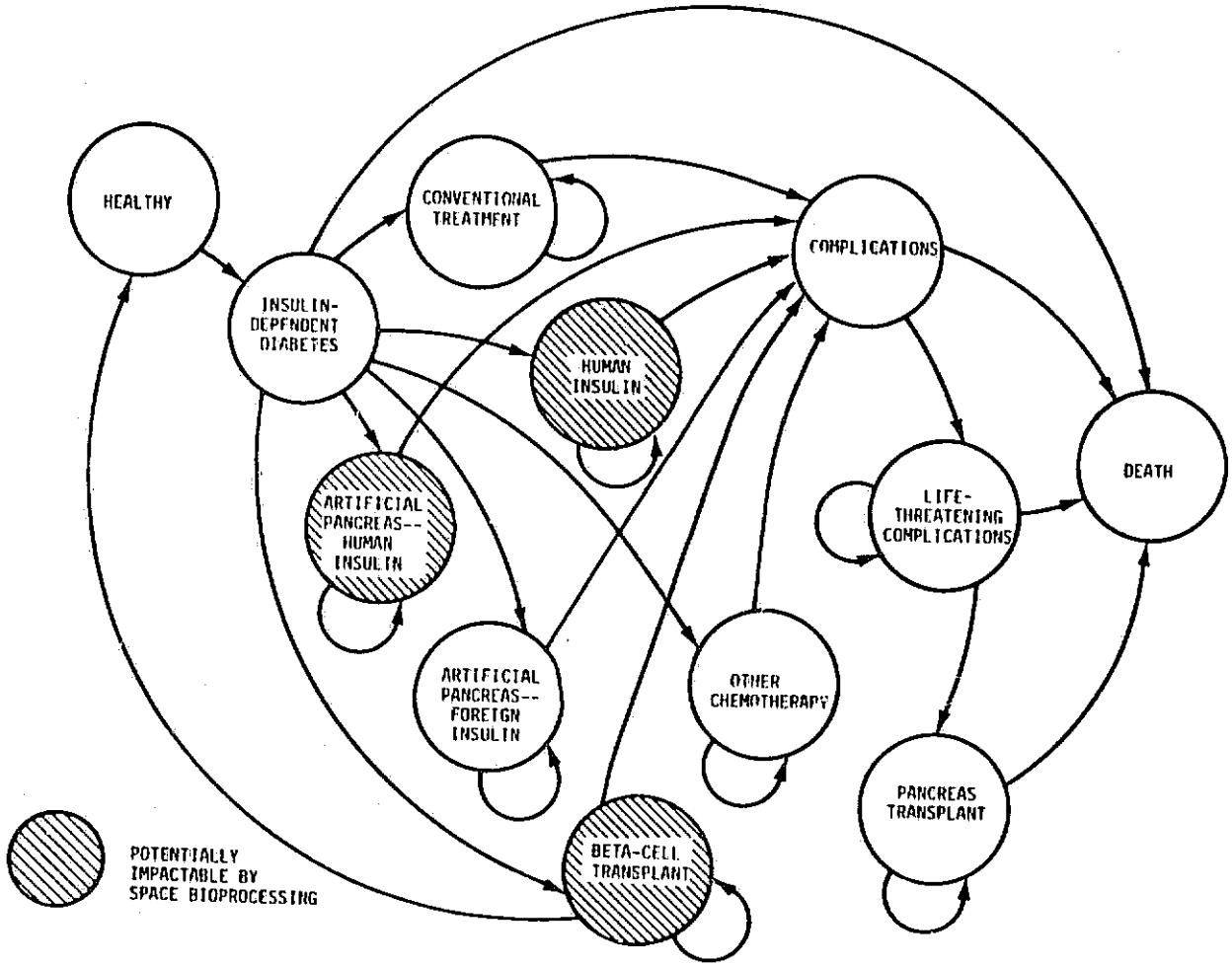
- PRODUCTION OF HUMAN INSULIN FOR DIABETICS
- TRANSPLANT OF BETA CELLS IN DIABETICS

BETA CELLS ISLETS OF LANGERHANS--SIMPLIFIED MODEL

The model illustrated here for the use of beta cell separations in the treatment of diabetes has been simplified. The actual transitions from state-to-state depend on the age of the patient at the onset of diabetes and the duration or length of time since disease onset. The inclusion of these factors make the model multi-dimensional.

It should be noted that other techniques, namely synthesis and the use of E. coli, are being researched for the production of human insulin. For the purposes of economic modeling the source of the human insulin is not consequential except as it affects the cost factors involved.

BETA CELLS ISLETS OF LANGERHANS--SIMPLIFIED MODEL



DIABETES INFORMATION REQUIREMENTS

The major causes of death among diabetics are cardiovascular and renal complications associated with the disease rather than diabetic coma. These complications are believed to arise from incomplete control of the blood sugar levels, antibody build-up against foreign insulin (i.e., animal insulin currently used), and possibly other as yet unknown factors. By affecting the degree of control and the antibody build-up, the use of human insulin is expected to reduce the incidence of complications and thus increase the life expectancy of the diabetic as well as reducing the actual cost of treating these complications and the productivity losses associated with morbidity due to diabetic complications.

Prevalence and incidence of diabetes, that is the total number of diabetics and the number of newly diagnosed diabetics in a given year in the United States by age at onset, will provide an estimate of the current patient population. This number may need to be adjusted to account for the change in that population which will occur before the new treatment is available.

Because the improvement due to the new treatment will come at least partly from a reduction in the severity or duration of complications, the prevalence and incidence of each complication by age at onset and duration is required. The mortality and morbidity losses measured by additional lost wages, lost earnings due to illness and medical expenses associated with the treatment of complications in terms of a percentage of the patient population incurring the cost of sickness or early death associated with the disease itself and its complications (again by age at onset and duration) are necessary to establish the baseline case from which to measure benefits.

The indirect benefit will then be measured by estimating the improvement due to each new treatment, in reduced transitional probabilities of going from a treatment state to a treatment plus complication state by age at onset and duration, and comparing the total indirect resulting costs to the indirect costs associated with conventional treatment.

Direct (economic) benefits will be measured by comparing the cost of present treatment (insulin, medical supplies, physician visits, tutoring, diet changes, etc.) to the estimated cost of the new treatments (including the cost of separations, tissue culture, other handling costs, plus medical supplies, physician visits, etc.) It is important to note that in the case where a new treatment is more expensive than conventional treatment, the direct benefit may be negative. It is hoped that in such cases, indirect benefits will outweigh direct losses. If this is not the case, the space processing experiment should not be undertaken unless other social or scientific factors can be shown to outweigh economic losses.

DIABETES INFORMATION REQUIREMENTS

PREVALENCE AND INCIDENCE OF DIABETES BY AGE OF PATIENT AT ONSET

PREVALENCE AND INCIDENCE OF COMPLICATIONS BY AGE AT ONSET AND DURATION OF DIABETES

COSTS OF TREATMENT BY TYPE

DIRECT AND INDIRECT COST OF TREATING DIABETES AND ITS COMPLICATIONS

MORTALITY RATES BY COMPLICATION AND ASSOCIATED COSTS

EXPECTED IMPROVEMENT IN MORTALITY AND MORBIDITY DUE TO TREATMENT TYPES

DIABETES MAJOR DATA SOURCES

Data on diabetes is reasonably complete and readily available. Dr. C.J. Van Oss was contacted on the actual electrophoretic process. The other doctors listed, as well as many others, have been contacted with respect to the disease itself and the expected improvements due to individual treatments.

DIABETES MAJOR DATA SOURCES

- INFORMATION SOURCES

  C.J. VAN OSS - STATE UNIVERSITY OF NEW YORK

  M. MACGILLIVRAY - BUFFALO CHILDRENS HOSPITAL

  W. CHICK - JOSLIN CLINIC

  D. MARTIN - MASSACHUSETTS GENERAL HOSPITAL

  J.S. NAJARIAN - UNIVERSITY OF MINNESOTA

- STATISTICAL SOURCES

  REPORT OF THE NATIONAL COMMISSION ON DIABETES TO THE CONGRESS OF THE UNITED STATES, NATIONAL INSTITUTES OF HEALTH

  DIABETES MELLITUS, NATIONAL INSTITUTES OF HEALTH

  DIABETES SOURCE BOOK, U.S. PUBLIC HEALTH SERVICE

  MORBIDITY AND MORTALITY IN DIABETICS IN THE FARMINGTON POPULATION SIXTEEN-YEAR FOLLOW-UP STUDY, GARCIA, ET AL.

  JOSLIN'S DIABETES MELLITUS, MARBLE, ET AL.

  CHANGES IN THE COSTS OF TREATMENT OF SELECTED ILLNESSES, SCITOVSKY AND MCCALL

  THE ECONOMIC COST OF ILLNESS REVISITED, COOPER AND RICE

  DIABETES AND ITS MANAGEMENT, OAKLEY, PYKE AND TAYLOR

STEM CELLS

Stem cells are the young cells which later develop into other cells of the body but yet have no self-recognition and therefore strongly reduce immunological rejection. It is believed that stem cells could be transplanted in the patient to develop into and replace the specific type of cell causing an immunological problem. The transplant of stem cells to establish a compatible immune system to reduce rejection in organ transplants has been selected as an illustrative example. Benefits of this use would accrue from increased life expectancy, decreased morbidity and increased availability of donor organs to the patient in need of a transplant.

STEM CELLS

- YOUNG CELLS, NO SELF-RECOGNITION
- PRECURSOR CELLS, DEVELOP INTO OTHER TYPES
- SEPARATION INTO PURE POPULATIONS FOR STUDY AND TRANSPLANT

POSSIBLE USES IN TREATMENT OF

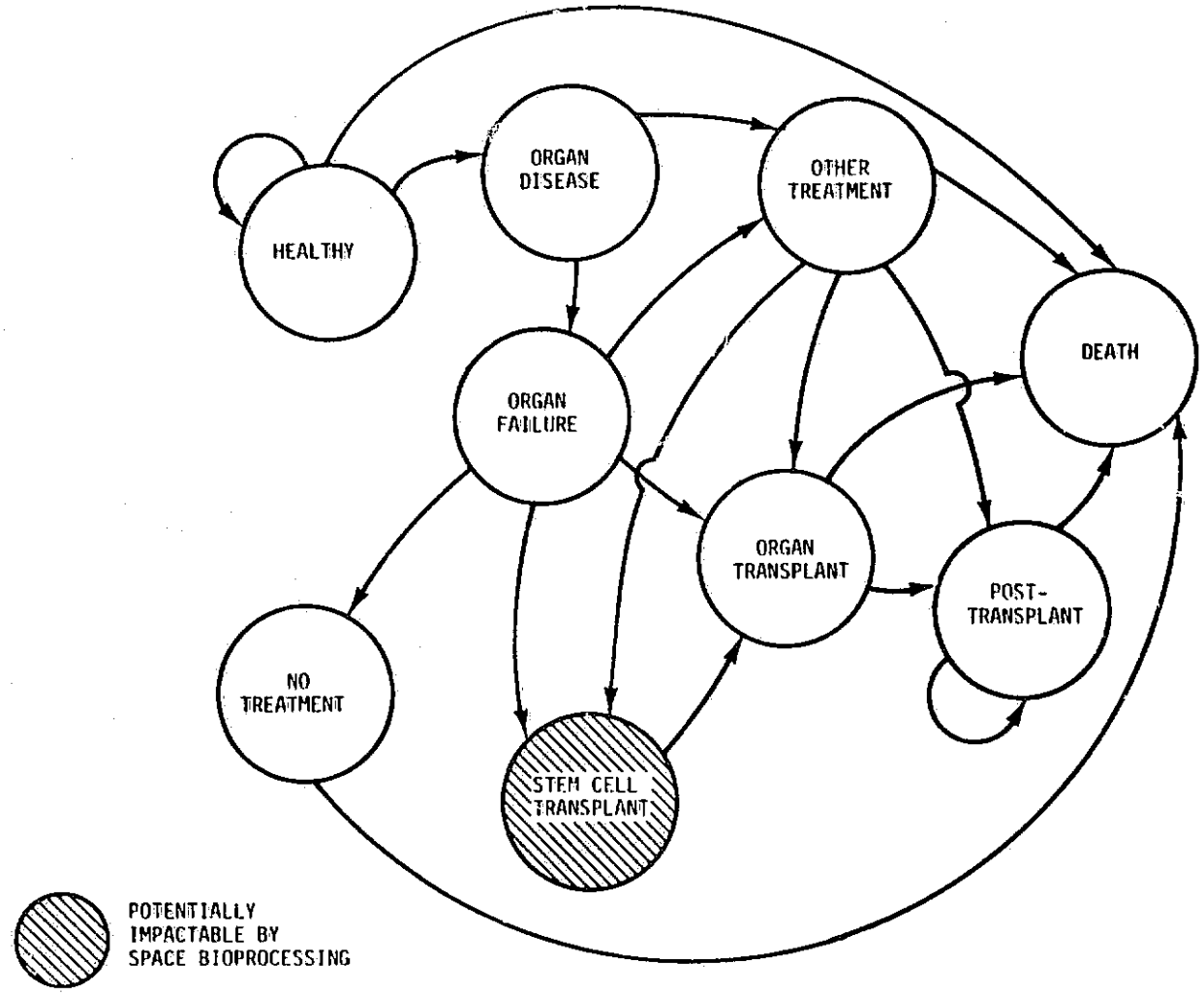
- CANCERS
- APLASTIC ANEMIA
- ESTABLISHMENT OF IMMUNE SYSTEM FOR SUBSEQUENT ORGAN TRANSPLANT
- LEUKEMIA AND LYMPHOMA

INDICATES USE TAKEN AS EXAMPLE FOR THIS STUDY

STEM CELLS TRANSITIONAL PROBABILITY MODEL

The basic transitional probability model for the establishment of an immune system as a prelude to organ transplants is shown here. Actual transitional probabilities will vary according to the type of transplant, type of donor (live or cadaver, related or nonrelated individual, etc.) and perhaps other factors such as the age of the patient. Many such conditions could add an additional dimension to the model so that the final model is expected to be more complex than indicated here.

STEM CELLS TRANSITIONAL PROBABILITY MODEL



STEM CELLS INFORMATION REQUIREMENTS

Since the new treatment using stem cell transplant may allow more patients to have transplants than is now possible, the number of desired (medically justifiable) transplants is required. The expected improvements in mortality, morbidity and organ availability will very likely come from the estimations of experts in the field.

STEM CELLS INFORMATION REQUIREMENTS

NUMBER OF TRANSPLANTS REQUIRED BY TYPE

NUMBER OF TRANSPLANTS NOW GIVEN BY TYPE OF DONOR

AVERAGE LIFE EXPECTANCY BY TYPE OF TRANSPLANT AND TYPE OF DONOR

AVERAGE MORBIDITY ASSOCIATED WITH EACH CATEGORY OF TRANSPLANTS

COST OF TRANSPLANTS, OTHER TREATMENTS, AND POSTTRANSPLANT CARE

EXPECTED COST OF STEM CELL TRANSPLANT

EXPECTED IMPROVEMENT IN MORTALITY AND MORBIDITY WITH STEM CELL TRANSPLANT

EXPECTED IMPROVEMENT IN ORGAN AVAILABILITY

DEMOGRAPHIC CHARACTERISTICS OF TARGET PATIENT POPULATION

STEM CELLS MAJOR DATA SOURCES

Dr. Johnson is a specialist in the separation of blood cells. Doctors Gale and Cline were among those contacted with respect to the blood cell aspects of the proposed treatment and Dr. Rubin is a major source on kidney transplants and related problems.

Statistical data on the current use of transplants exists and is commonly available. Information on the desired number of transplants will have to be extracted from statistical sources on the diseases requiring such treatment.

STEM CELLS MAJOR DATA SOURCES

INFORMATION SOURCES

A. JOHNSON, NEW YORK UNIVERSITY

R. GALE, UNIVERSITY OF CALIFORNIA AT LOS ANGELES

M. CLINE, UNIVERSITY OF CALIFORNIA AT LOS ANGELES

A. RUBIN, ROGOSIN KIDNEY CENTER, NEW YORK HOSPITAL

STATISTICAL SOURCES

ACUTE CONDITIONS, INCIDENCE AND ASSOCIATED DISABILITY, UNITED STATES, JULY 1973-JULY 1974, HEALTH RESOURCES ADMINISTRATION

HOSPITAL DISCHARGES AND LENGTH OF STAY: SHORT-STAY HOSPITALS, UNITED STATES, 1972, HEALTH RESOURCES ADMINISTRATION

REPORT TO CONGRESS: TREATMENT OF CHRONIC KIDNEY FAILURE: DIALYSIS, TRANSPLANT, COST AND THE NEED FOR MORE VIGOROUS EFFORTS, G.A.O.

TWELFTH REPORT OF THE HUMAN RENAL TRANSPLANT REGISTRY, ADVISORY COMMITTEE OF THE RENAL TRANSPLANT REGISTRY

BLOOD DONOR CHARACTERISTICS AND TYPES OF BLOOD DONATIONS, UNITED STATES, 1973, HEALTH INTERVIEW SURVEY

TRANSPLANTS: SHORTAGE OF DONORS IS STILL ACUTE, 1977, L. K. ACTMAN

MEGAKARYOCYTES

Megakaryocytes are the large multineucleated cells of the bone marrow which produce platelets. Some diseases, and certain types of drugs or radiation cause a reduction in platelet production. Currently this condition is treated with the transfusion of platelets. It is only possible to sustain life in a patient whose body is not producing platelets by transfusion of platelets for one (to a maximum at times of two) weeks. Ten percent of the blood currently collected by blood banks, etc., is used for platelet production. Transplanting megakaryocytes to restore a patient's production of platelets could extend the life of these patients substantially.

In addition, if platelet production could be restored in this manner, more aggressive use could be made of current chemotherapy and irradiation techniques, thus reducing mortality and morbidity costs of the original illness.

The boxed applications are the treatments selected for use as examples in this report.

MEGAKARYOCYTES

- PRODUCE PLATELETS
- CURRENTLY TRANSFUSE PLATELETS
- PLATELET TRANSFUSION NOW ONLY POSSIBLE FOR 1 WEEK
- LARGE PORTION OF BLOOD COLLECTED FOR PLATELETS

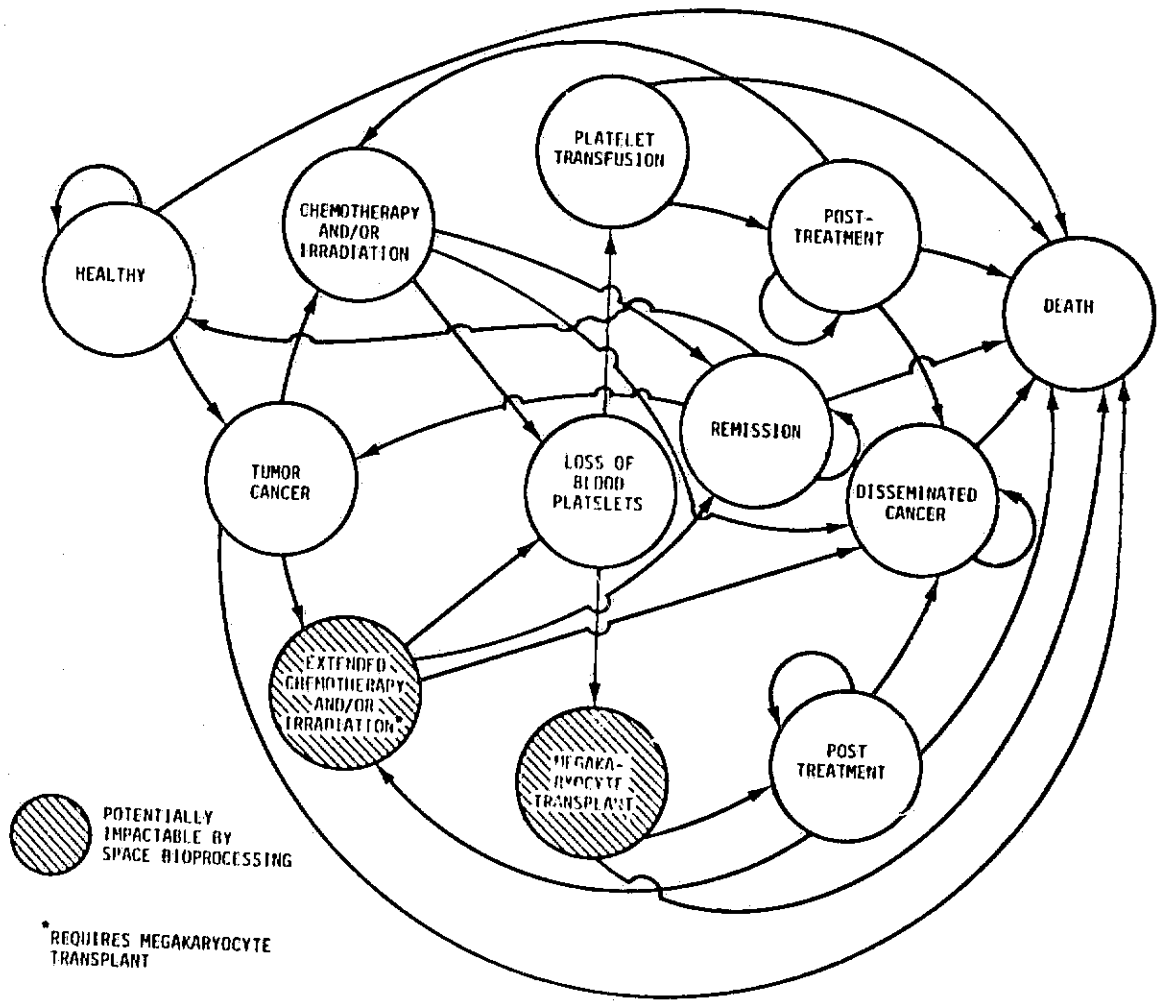
POSSIBLE APPLICATIONS

- TRANSFUSION FOLLOWING CHEMOTHERAPY AND IRRADIATION TECHNIQUES FOR TUMOR CANCERS (NOT DISSEMINATED CANCERS)
- EXTENSION OF CURRENT TECHNIQUES AGAINST TUMOR CANCERS OR APLASTIC ANEMIAS
- PLATELET REPLACEMENT AFTER DESTRUCTION BY CERTAIN ANTI-INFLAMMATORY DRUGS

MEGAKARYOCYTE TRANSITIONAL PROBABILITY MODEL

This figure illustrates the transitional probability model applicable to the transplant of megakaryocytes. Note that benefits can be derived from the use of megakaryocyte transplants with or without the extended or more aggressive use of chemotherapy and/or irradiation.

MEGAKARYOCYTE TRANSITIONAL PROBABILITY MODEL



MEGAKARYOCTYE INFORMATION REQUIREMENTS

PREVALENCE AND INCIDENCE OF TUMOR CANCERS BY SITE

CURRENT USE OF CHEMOTHERAPY AND IRRADIATION BY SITE

CURRENT USE OF PLATELET TRANSFUSION

CURRENT MORBIDITY AND MORTALITY RATES AND ASSOCIATED COSTS

COST OF CURRENT TREATMENTS .

EXPECTED IMPROVEMENTS FROM MEGAKARYOCYTE TRANSPLANT

EXPECTED IMPROVEMENTS FROM EXTENDED USE OF CHEMOTHERAPY AND IRRADIATION

EXPECTED COST OF NEW TECHNIQUES

MEGAKARYOCYTE MAJOR DATA SOURCES

Data on the existing use and costs of chemotherapy and irradiation are exceptionally good. Data collected and published by the federal government are probably better on cancers than on any other class of diseases. The information on the possibilities of extending current treatments and expected improvements in patient survival and cost reductions due to space-based treatments seems relatively obtainable from the experts listed here as well as others concerned with the problem.

MEGAKARYOCTYES MAJOR DATA SOURCES

INFORMATION SOURCES

A. JOHNSON, NEW YORK UNIVERSITY

B. CLARKSON, COMPREHENSIVE CANCER CARE CENTER

R. GALE, UCLA

H. HEISE, NATIONAL INSTITUTES OF HEALTH

STATISTICAL SOURCES

CANCER PATIENT SURVIVAL REPORT NUMBER 5, 1976, NATIONAL INSTITUTES OF HEALTH

THIRD NATIONAL CANCER SURVEY: HOSPITALIZATIONS AND PAYMENTS TO HOSPITALS, NATIONAL INSTITUTES OF HEALTH

THIRD NATIONAL CANCER SURVEY: INCIDENCE DATA, NATIONAL CANCER INSTITUTE, NIH

VITAL STATISTICS OF THE UNITED STATES, HEALTH RESOURCES ADMINISTRATION

GRANULOCYTES

As with the treatment of tumor cancers, the major problem associated with treatment of acute leukemias by chemotherapy and/or irradiation techniques is bone marrow toxicity. Currently this problem in leukemias is treated by whole bone marrow transplants. Such transplants give the patient a mixture of blood cells, some of which are needed, others of which are not. Selective transplant is expected to improve the survival rate of these patients.

It is not expected that this technique would be used for patients (usually children) with acute lymphoblastic leukemia until after remission and subsequent relapse because the survival rate of patients before the first relapse is quite high.

In a manner similar to that described for megakaryocyte transplants, the use of chemotherapy and/or irradiation could be made more aggressive by the use of granulocyte transfusions.

GRANULOCYTES

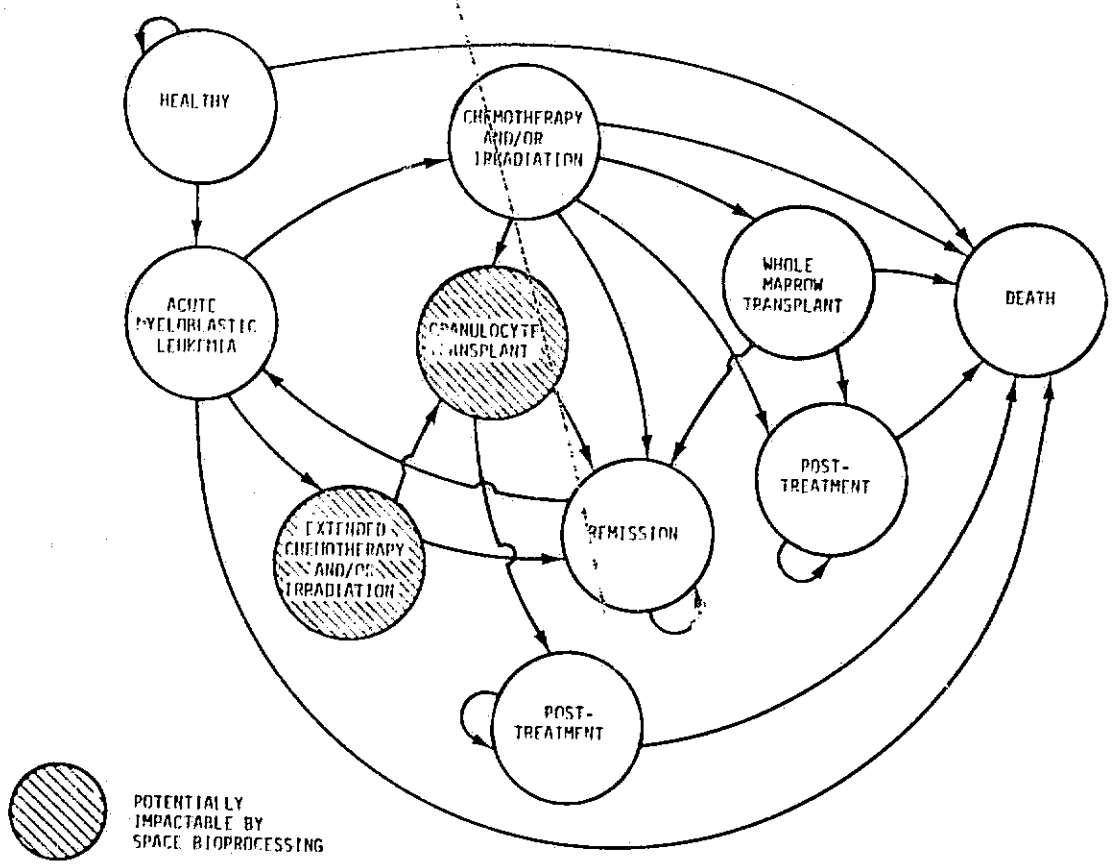
- 50 to 70% OF BLOOD CELLS
- REDUCE MAJOR PROBLEM OF MARROW TOXICITY IN CHEMOTHERAPY AND/OR IRRADIATION

POSSIBLE USES

- TRANSFUSION FOLLOWING CHEMOTHERAPY AND/OR IRRADIATION FOR ACUTE MYELOBLASTIC LEUKEMIA (AML, PRIMARILY ADULT)
- TRANSFUSION FOLLOWING CHEMOTHERAPY AND/OR IRRADIATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA (PRIMARILY CHILDHOOD) AFTER RELAPSE
- EXTENTION OF CHEMOTHERAPY AND/OR IRRADIATION TECHNIQUES

Once again, note from the transitional probability model, that benefits could be estimated with and without the use of more aggressive (extended) chemotherapy and/or irradiation treatment of acute leukemias.

GRANULOCYTE TRANSITIONAL PROBABILITY MODEL



GRANULOCYTE INFORMATION REQUIREMENTS

PREVALENCE AND INCIDENCE OF ACUTE MYELOBLASTIC LEUKEMIA

NUMBER OF CASES TREATED WITH CHEMOTHERAPY AND IRRADIATION ANNUALLY AND AVERAGE NUMBER OF COURSES PER YEAR PER CASE

COST OF PRESENT TREATMENT

NUMBER OF CASES NOT ADEQUATELY CONTROLLED BY PRESENT TREATMENT

CURRENT MORTALITY AND MORBIDITY RATES

EXPECTED IMPROVEMENTS DUE TO IMPROVED TRANSPLANTS

EXPECTED REDUCTION IN MORBIDITY AND MORTALITY DUE TO INCREASED USE OF CHEMOTHERAPY AND IRRADIATION

EXPECTED COST OF IMPROVED TRANSPLANTS AND EXTENDED TREATMENTS

GRANULOCYTES MAJOR DATA SOURCES

Data on leukemias and the current treatments for leukemias are quite readily available. Large amounts of research are being conducted on possible treatments or improvements in treatments for leukemic patients. Information on the need for extended use of these treatments will need to be developed from the mortality rates of present leukemic patients and expert opinion on the relative expected improvements in the treatments.

GRANULOCYTES MAJOR DATA SOURCES

INFORMATION SOURCES

R. GALE, UCLA

E. HENDERSON, ROSWELL PARK MEMORIAL INSTITUTE

C. J. VAN OSS, STATE UNIVERSITY OF NEW YORK

H. HEISE, NATIONAL INSTITUTES OF HEALTH

STATISTICAL SOURCES

ANNUAL REPORTS: CANCER FACTS AND FIGURES, 1969-1977, AMERICAN CANCER SOCIETY

RECENT RESULTS IN CANCER RESEARCH, ADVANCES IN THE TREATMENT OF ACUTE (BLASTIC) LEUKEMIAS, MATHE, EDITOR

PROGRESS AGAINST LEUKEMIAS, LYMPHOMAS AND MULTIPLE MYELOMA, NATIONAL CANCER INSTITUTE

CANCER PATIENT SURVIVAL REPORT NUMBER 5, 1976, NATIONAL INSTITUTES OF HEALTH

THIRD NATIONAL CANCER SURVEY: HOSPITALIZATIONS AND PAYMENTS TO HOSPITALS, NATIONAL INSTITUTES OF HEALTH

THIRD NATIONAL CANCER SURVEY: INCIDENCE DATA, NATIONAL CANCER INSTITUTE, NIH

PLASMA CELLS

Because plasma cells are noncirculating and found in solid masses in the body, they are not readily available for study or therapeutic use. The only available plasma cells are taken from tumors, and thus may reflect strong abnormalities. Plasma cells are formed from the B-lymphocytes and form an integral part of the immune system. Patients without plasma cells lack the ability to fight infection, particularly bacterial infections. While the condition itself (of lacking plasma cells, i.e., hypoagammaglobulinemia) is not fatal, very often the infections, which generally follow, are. The example taken here is that of plasma cell transplants for patients with acquired hypoagammaglobulinemia. This disease is generally acquired after chemotherapy, irradiation or accidents. Most of the other diseases showing a severe reduction in plasma cells are actually diseases involving the B-lymphocytes, thus the secondary affect on plasma cells.

PLASMA CELLS

PLASMA CELLS

- NONCIRCULATING
- CURRENTLY STUDY LIMITED TO TUMOR PLASMA CELLS
- MADE FROM B LYMPHOCYTES

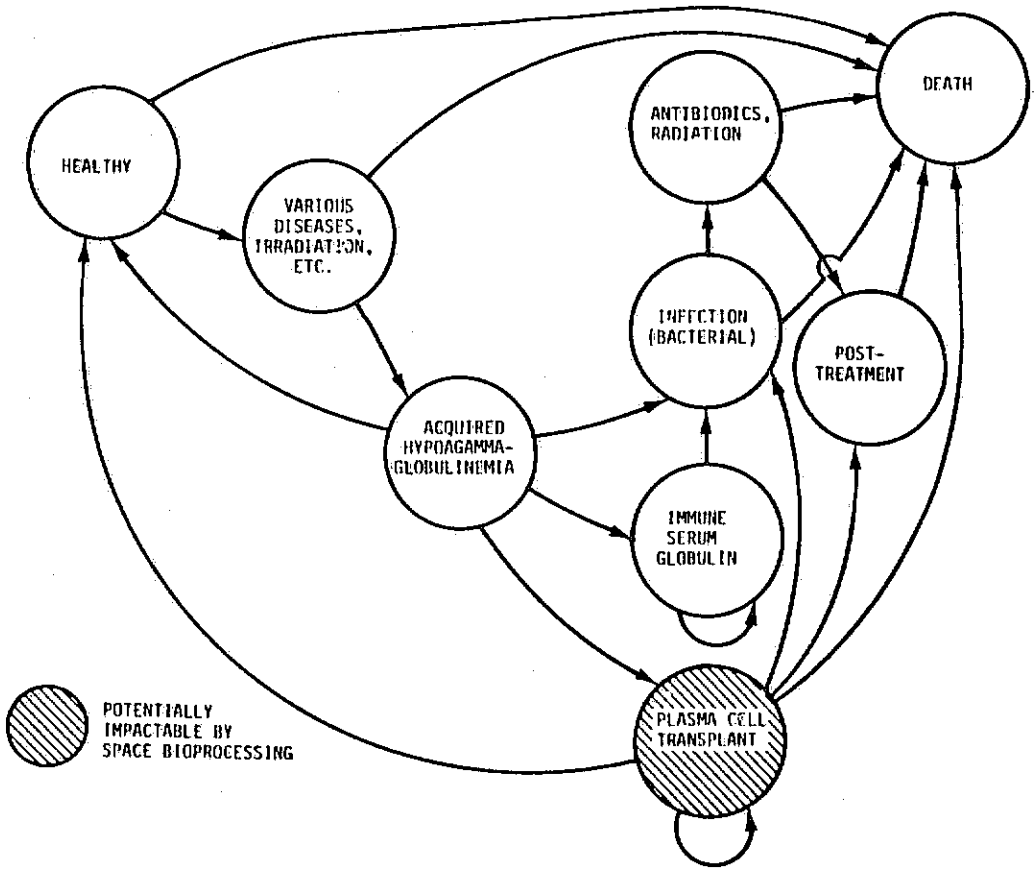
POSSIBLE USES

- ACQUIRED AGAMMAGLOBULINEMIA
- OTHER DISEASES SHOWING ABSENCE OF B LYMPHOCYTES

PLASMA CELLS TRANSITIONAL PROBABILITY MODEL

The transitional probability model shown here for the transplant of plasma cells in treatment of acquired hypoagammaglobulinemia illustrates the general course of the disease and the expected change in that pattern with the introduction of a new treatment type. Onset of the disease is usually related to other health problems. One of the potential difficulties in modeling this new treatment is the determination of the actual target patient population size. It is possible that in many cases, the patient under chemotherapy irradiation, etc., is believed to die of an infection, and agammaglobulinemia which may have existed is either not diagnosed or not recorded. Another possible difficulty lies in the fact that a few patients have a spontaneous reversal of hypoagammaglobulinemia. (Note arrow from acquired hypoagammaglobulinemia to healthy.) Care must be taken that these remissions are not attributed to any treatment method.

PLASMA CELLS TRANSITIONAL PROBABILITY MODEL



PLASMA CELLS INFORMATION REQUIREMENTS

Information requirements for the modeling of the new treatment with plasma cells are very similar to those of the other substances. However, since so little is known about healthy plasma cells, it is difficult to know how long the cells will survive once separated from the solid masses of which they are a part. In light of this it will be necessary to gather more information on the length of time a single transplant operation can be expected to remain clinically effective. Due to the experimental aspects of this problem, expert opinion is likely to be the best source of this information.

PLASMA CELLS INFORMATION REQUIREMENTS

INCIDENCE AND PREVALENCE OF ACQUIRED HYPOAGAMMAGLOBULINEMIA

ASSOCIATED MORBIDITY AND MORTALITY

COST OF CURRENT TREATMENT (MONTHLY I.M. IMMUNE SERUM GLOBULIN)

EXPECTED IMPROVEMENT IN MORBIDITY AND MORTALITY DUE TO PLASMA CELL TRANSPLANT

EXPECTED COST OF PLASMA CELL TRANSPLANT

EXPECTED LENGTH OF TREATMENT EFFECTIVENESS

PLASMA CELL MAJOR DATA SOURCES

Because of the relative infrequency of the recording of hypoagammaglobulinemia, expert opinion may be needed to correlate more general data to the prevalence and incidence of the disease.

PLASMA CELLS MAJOR DATA SOURCES

INFORMATION SOURCES

A. JOHNSON, NEW YORK UNIVERSITY

R. GALE, UCLA

M. CLINE, UCLA

H. HEISE, NATIONAL INSTITUTES OF HEALTH

STATISTICAL SOURCES

PATIENTS RECEIVING CHEMOTHERAPY, LETTER, H. HEISE

VITAL STATISTICS OF THE UNITED STATES, HEALTH RESOURCES ADMINISTRATION

ACUTE CONDITIONS, INCIDENCE AND ASSOCIATED DISABILITY, HEALTH INTERVIEW SURVEY

BLOOD DONOR CHARACTERISTICS AND TYPES OF BLOOD DONATIONS, UNITED STATES, 1973, HEALTH INTERVIEW SURVEY

PURIFIED PEPTIDE HORMONES: CLINICAL APPLICATIONS

The application of space bioprocessing to the peptide hormones listed here is somewhat different than its application in the other candidate substance areas in that it involves the electrophoretic purification of synthetic hormones rather than the separation of naturally occurring cells. Each of the first four substances listed here has a relatively well known clinical application; however, difficulties in extracting animal material or in purifying synthetic materials have limited their use. Purification of synthetic materials is particularly difficult because the impurities tend to be so similar to the desired substance (such as a slight rearrangement of the peptide bonds) that normal chemical separation methods are not adequate.

The separation of these hormones may have additional scientific value in that economically feasible purification of these hormones would encourage synthesis and purification of other, more complex hormones which, hitherto, have not been undertaken due to anticipated purification problems.

ACTH has been chosen as an example because it seems to be the most promising of the polypeptide hormones studied to date. It is used to withdraw patients from steriod therapies.

Secretin is useful in the control of gastric secretions in stress ulcers. Recently a drug, cimetidine, has been introduced to the market which exhibits similar control characteristics. Since cimetidine is not a peptide hormone, it can be taken orally without loss of effectiveness and is therefore also much more convenient to use than secretin would be. (Personal conversation with Dr. Morton Grossman, VA Hospital, Los Angeles.)

Calcitonin and oxytocin are currently used clinically as noted. Small patient populations and relatively small expected improvements in the product lead us not to recommend these substances for further benefit study.

Beta endorphin is a newly discovered substance which is thought to control certain actions of the b... A number of research projects are continuing in order to determine beta endorphin's impact on the emotionally disturbed. These efforts show great promise and should be followed closely to determine the desirability of benefit studies in this area.

PURIFIED PEPTIDE HORMONES: CLINICAL APPLICATIONS

ADRENOCORTICOTROPIC HORMONE (ACTH)

- POST-STEROID THERAPY

SECRETIN

- REGULATION OF GASTRIC SECRETIONS IN DUODENAL ULCERS

CALCITONIN

- TREATMENT OF BONE DEGENERATIVE DISEASES

OXYTOCIN

- INDUCTION OF LABOR AND MILK EJECTION

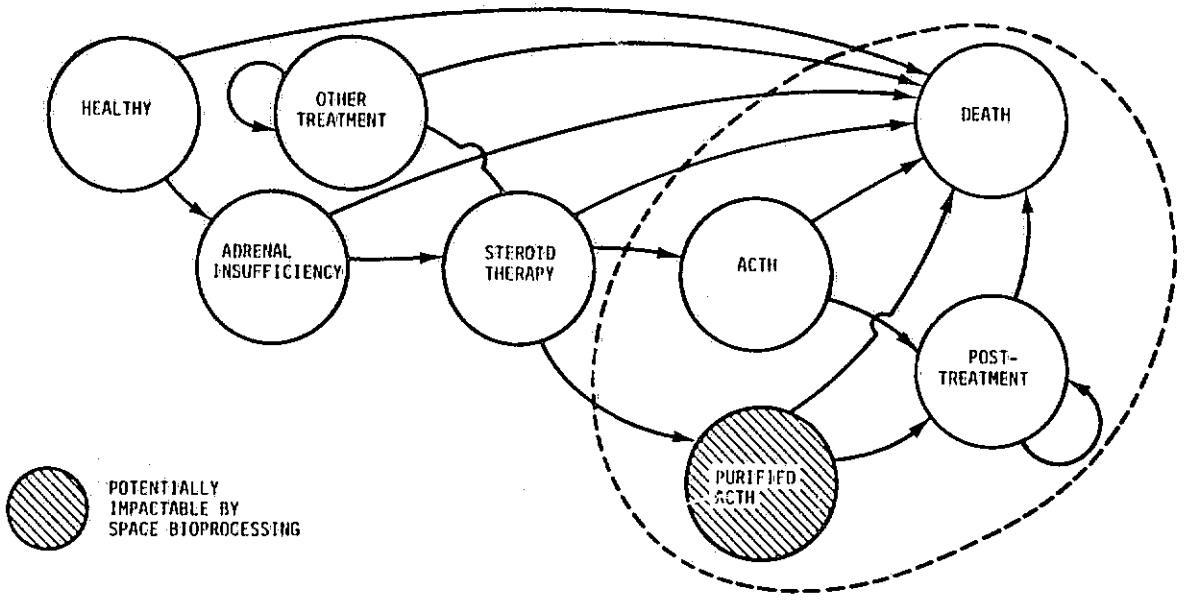
BETA ENDORPHIN

- REGULATION OF PATIENTS WITH SEVERE PSYCHOLOGICAL STRESS

ACTH TRANSITIONAL PROBABILITY MODEL

The transitional probability model for ACTH is much simpler than many of the other models. It is very important to remember that the benefits of the new treatment will be (in addition to actual cost differences) the reduction in morbidity and mortality associated with the improvement in the ACTH rather than the use of ACTH as a post-steroid treatment. Precautions must be taken to avoid confusion with these types of morbidity and mortality (i.e., that associated with the use of ACTH), and the morbidity and mortality associated with steroid treatments and the diseases requiring such therapy. The dashed circle indicates the relevant portion of the process and that portion with which the model will deal specifically.

ACTH TRANSITIONAL PROBABILITY MODEL



ACTH INFORMATION REQUIREMENTS

INCIDENCE OF STEROID THERAPY

NUMBER OF PATIENTS WITHDRAWN ANNUALLY WITH ACTH

MORBIDITY AND MORTALITY ASSOCIATED WITH THE USE OF ACTH

COST OF ACTH TREATMENT

EXPECTED IMPROVEMENTS DUE TO PURIFICATION OF ACTH

EXPECTED COST OF ACTH PURIFICATION

ACTH MAJOR DATA SOURCES

INFORMATION SOURCES

M. BIER, UNIVERSITY OF ARIZONA

L. BARSTOW, VEGA BIOCHEMICAL CORPORATION

J. POTTS, MASSACHUSETTS GENERAL HOSPITAL

R. COLSCOTT, ARMOUR PHARMACEUTICAL CO.

M. GROSSMAN, VA HOSPITAL, LOS ANGELES

STATISTICAL SOURCES

HOSPITAL DISCHARGES AND LENGTH OF STAY: SHORT-STAY HOSPITALS, UNITED STATES, HEALTH INTERVIEW SURVEY

CLINICAL EVALUATION OF HORMONAL EXCESS AND DEFICIENCY, JANOWITZ, ET AL.

CURRENT INDUSTRIAL REPORTS, PHARMACEUTICAL PREPARATIVES, U.S. DEPARTMENT OF COMMERCE

METHODS IN INVESTIGATIVE AND DIAGNOSTIC ENDOCRINOCOGY: PEPTIDE HORMONES, BERSON AND YALOW

LYMPHOCYTES

One possible use of the separation of lymphocytes into subgroups has already been studied by ECON in the application of lymphocytes in the therapy of End Stage Renal Disease (Contracts NASW-2558 and NAS-9-15338). Since lymphocytes are so important in the body, there are many other possible applications of pure lymphocyte subgroup populations. Some of these are listed here. The study involving the autoimmune diseases, specifically rheumatoid arthritis, has been selected as an example because it is least similar to the processes described earlier in this report for other blood cell separations.

Rheumatoid arthritis is a disease in which the body recognizes certain of its own cells as foreign. An immune reaction takes place causing inflammation, pain and eventual deformity of the affected joints. The transfusion of lymphocytes could reduce or arrest this reaction.

LYMPHOCYTES

- ALREADY STUDIED IN END STAGE RENAL DISEASE
- MANY OTHER POSSIBLE USES

OTHER POSSIBLE APPLICATIONS

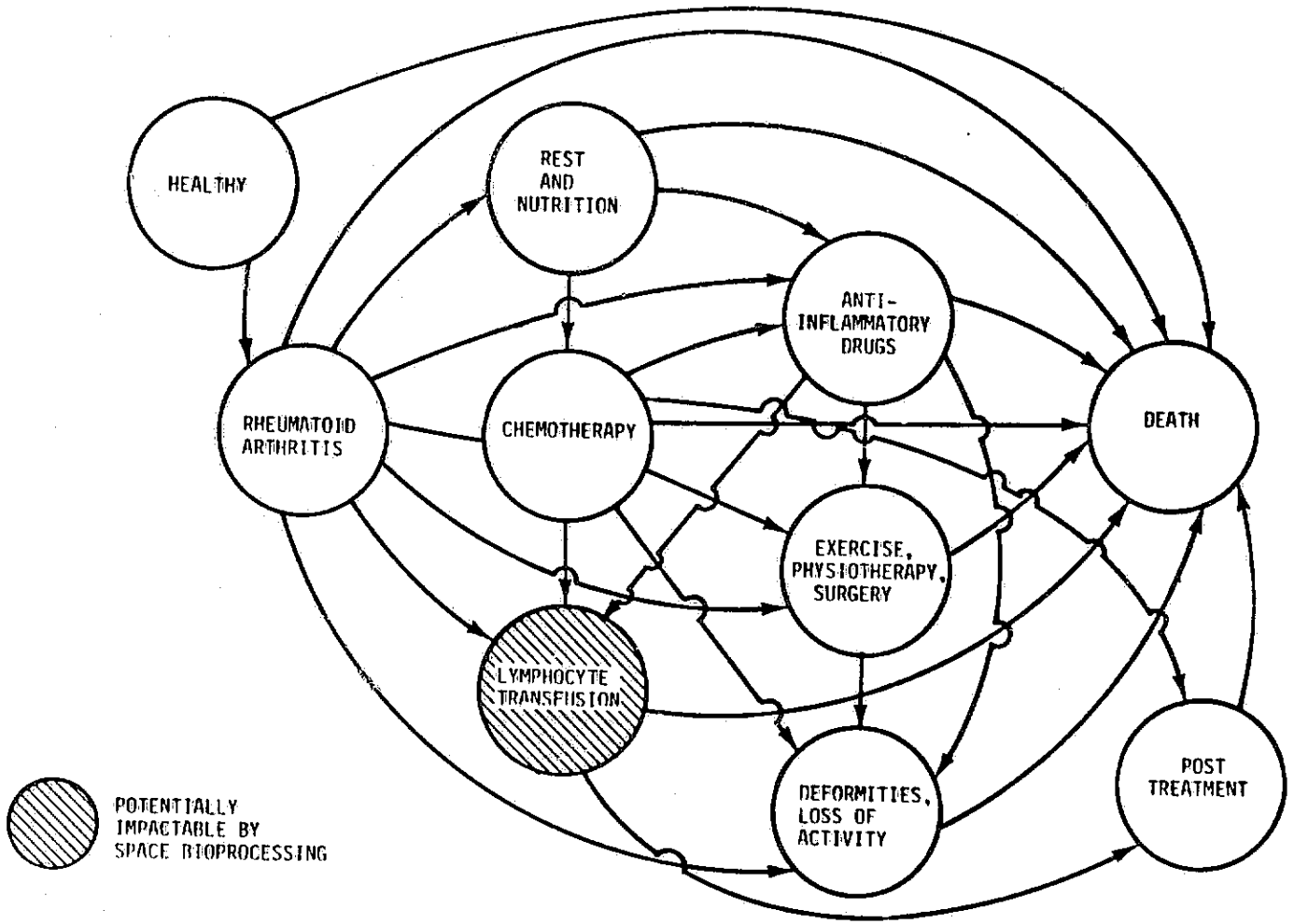
- IMMUNE SYSTEM DISEASES (E.G., AGAMMAGLOBULINEMIA)
- CANCERS
- AUTOIMMUNE DISEASES (E.G., RHEUMATOID ARTHRITIS)

LYMPHOCYTE TRANSITIONAL PROBABILITY MODEL

The transitional probability model for the use of lymphocyte transfusion in rheumatoid arthritis is complicated by the large number of treatment states. The model depicted here has been simplified. In many cases, transitions from one state to another may also be reversed, such as an individual moving from the use of anti-inflammatory drugs to exercise, physiotherapy or surgery back to the use of anti-inflammatory drugs. As a result of limitations of space and the desire to avoid confusion on the major progression of the disease, these repetitive transition routes have been omitted from this graphic representation, but to the extent which data is available such routes will be included in the model.

After consideration of the actual data, this model may be complicated further by the introduction of dimensions reflecting patient age and the duration of rheumatoid arthritis. (This would be similar to the process described for the use of the Beta Cells of the Islets of Langerhans in Diabetes Mellitus.)

LYMPHOCYTE TRANSITIONAL PROBABILITY MODEL



LYMPHOCYTES INFORMATION REQUIREMENTS

PREVALENCE AND INCIDENCE OF RHEUMATOID ARTHRITIS BY CURRENT TREATMENT AND PATIENT AGE

MORTALITY AND MORBIDITY ASSOCIATED WITH DISEASE AND TREATMENTS

COST OF CURRENT TREATMENTS

EXPECTED IMPROVEMENT DUE TO LYMPHOCYTE TRANSFUSION

EXPECTED COST OF LYMPHOCYTE TRANSFUSION

LYMPHOCYTES MAJOR DATA SOURCES

Data on rheumatoid arthritis are relatively complete and readily available due, at least in part, to the large percentage of the target population which resides in public and private nursing homes. The disease does occur in younger patients and those not residing in nursing homes. So data must be closely monitored to insure the inclusion of these patient groups.

LYMPHOCYTES MAJOR DATA SOURCES

INFORMATION SOURCES

R. GALE, UCLA

M. CLINE, UCLA

C. VAN OSS, STATE UNIVERSITY OF NEW YORK

R. WILLIAMS, NATIONAL INSTITUTES OF HEALTH

STATISTICAL SOURCES

HEALTH CHARACTERISTICS OF PERSONS WITH CHRONIC ACTIVITY LIMITATION, UNITED STATES, HEALTH INTERVIEW SURVEY

RHEUMATOID ARTHRITIS IN ADULTS, UNITED STATES, HEALTH RESOURCES ADMINISTRATION

MEASURES OF CHRONIC ILLNESS AMONG RESIDENTS OF NURSING HOMES, HEALTH RECORDS SURVEY

CHARGES FOR CARE AND SOURCES OF PAYMENT FOR RESIDENTS IN NURSING HOMES, UNITED STATES, HEALTH RECORDS SURVEY

HGH PRODUCING CELLS

The separation of human growth hormone producing cells would allow the treatment of hypopituitary dwarfism with human growth hormone. Such treatment must be initiated before the bone age of 14. (Note: bone age not chronological age.) Clinical tests have been performed with HGH which have shown improvement in height gain and secondary sexual characteristics. However, since dwarfs lead lives of a relatively normal number of years, it is not believed that HGH therapy would provide benefits from the extension of life per se. (Personal conversation with Dr. Roberto Escamilla, University of California, San Francisco.) The dwarf population of the United States is estimated at 8 to 20 thousand in all age groups. (Personal conversation with Dr. Salvatore Raite, National Pituitary Agency.) Thus, the population of those with bone age less than fourteen and the incidence of hypopituitary dwarfism is an extremely small target patient population. Because a small population with only morbidity benefits will lead to small expected benefits, HGH producing cells are not recommended for further benefit study at this time.

There are many other possible uses for HGH treatment. For example, in the treatment of uremia in renal transplants, for reduction of hemorrhage in stress ulcers, in the treatment of myotonic types of muscular dystrophy and in the treatment of hypoglycemia of pituitary origin. (Personal conservation Dr. Paul Todd, Pennsylvania State University.) However, it is not believed that the mechanism of clinical improvement is sufficiently well understood in these applications to justify further benefit study at this time, but such a broad range of possible applications indicates the desire for continued research with this substance.

HUMAN GROWTH HORMONE (HGH) PRODUCING CELLS

HUMAN GROWTH HORMONE (HGH) PRODUCING CELLS

- MORBIDITY BENEFITS ONLY

POSSIBLE APPLICATION

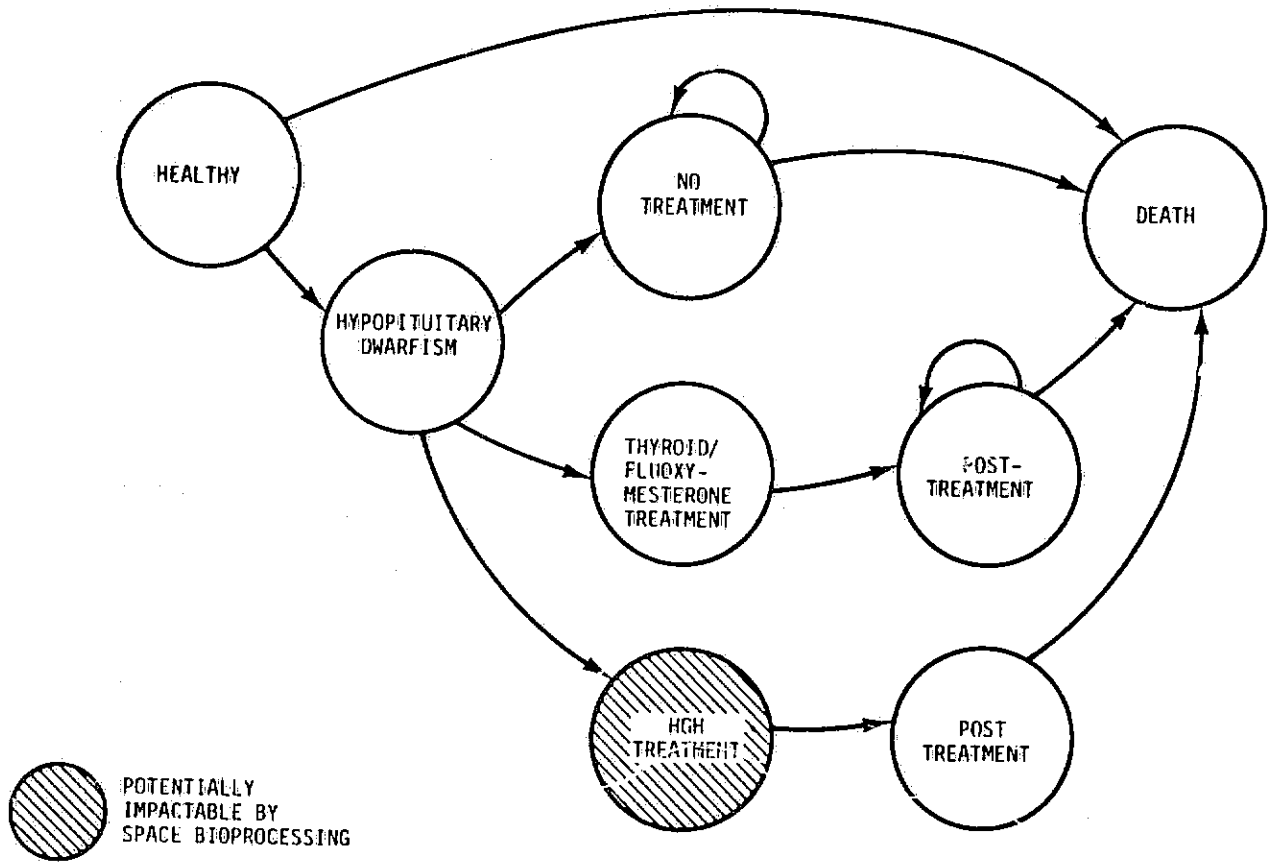
- TREATMENT OF YOUNG PATIENTS WITH HYPOPITUITARY DWARFISM, FAMILIAL SHORT STATUE, ETC.

HGH PRODUCING CELLS TRANSITIONAL PROBABILITY MODEL

As explained on previous slide, it is not believed that HGH treatment would affect the average life expectancy of dwarfs. Therefore, benefits from its use must be measured in terms of increased height with the associated increases in employability, reduced psychological stress, reduced cost of treatment and reduced need for expensive alterations to one's environment, and in terms of increased secondary sexual characteristics.

As with diabetes and rheumatoid arthritis, the modeling of this disease is complicated by a new dimension, in this case, patient bone age. This complication is not depicted here.

HUMAN GROWTH HORMONE PRODUCING CELLS
TRANSITIONAL PROBABILITY MODEL



HGH PRODUCING CELLS INFORMATION REQUIREMENTS

PREVALENCE AND INCIDENCE OF HYPOPITUITARY DWARFISM
BY BONE AGE OF PATIENT

COST OF TREATMENT BY TYPE

EXPECTED HEIGHT GAIN AND OTHER IMPROVEMENTS (E.G., APPEARANCE OF SECONDARY SEX CHARACTERISTICS) BY TREATMENT TYPE BY BONE AGE OF PATIENT AT TREATMENT BEGINNING

OTHER EXPECTED BENEFITS SUCH AS INCREASED EMPLOYABILITY AND REDUCED EXPENSES BY TREATMENT TYPE AND BONE AGE

HGH PRODUCING CELLS MAJOR DATA SOURCES

Data on the expected height gain from HGH treatment is readily available from the experimental results reported in the publications listed here. Information on the increased employability and other expected benefits is poor.

HGH PRODUCING CELLS MAJOR DATA SOURCES

INFORMATION SOURCES

P. TODD, PENNSYLVANIA STATE UNIVERSITY

S. RAITE, NATIONAL PITUITARY AGENCY

R. ESCAMILLA, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

G. RISA, LITTLE PEOPLE OF AMERICA

STATISTICAL SOURCES

CLINICAL STUDIES OF HUMAN GROWTH, HORMONE IN CHILDREN IN GROWTH PROBLEMS, R. ESCAMILLA

HUMAN GROWTH HORMONE, S. MASON, EDITOR

ADVANCES IN HUMAN GROWTH HORMONE RESEARCH, NATIONAL INSTITUTES OF HEALTH

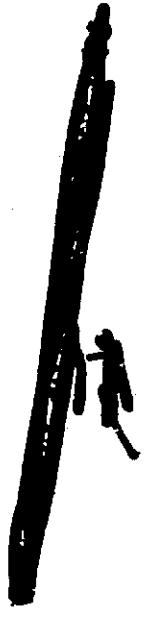
DISPROPORTIONATE SHORT STATUE, J. BAILEY

CONCLUSIONS AND RECOMMENDATIONS

NOT RECOMMENDED FOR FURTHER BENEFIT STUDY

The recommendation not to proceed at this time with further benefit study on any particular substance should not preclude further research of that substance based on scientific merit.

Each of these substances that are not recommended for further benefit study has been discussed in previous sections of this report.



NOT RECOMMENDED FOR FURTHER BENEFIT STUDY

- SECRETIN
  - + FOR CONTROL OF GASTRIC SECRETIONS IN STRESS ULCERS
  - + EQUAL IMPROVEMENT NOW AVAILABLE WITH USE OF CIMETIDINE
- CALCITONIN
  - + FOR USE IN BONE DEGENERATIVE DISEASES
  - + SMALL PATIENT POPULATION
- HGH PRODUCING CELLS
  - + FOR TREATMENT OF HYPOPITUITARY DWARFISM
  - + SMALL PATIENT POPULATION
  - + OTHER USES NOT CLEARLY DEFINED
- BETA ENDORPHIN
  - + FOR CONTROL OF SEVERE PSYCHOLOGICAL STRESS
  - + NEEDS FURTHER CLARIFICATION BEFORE FINAL RECOMMENDATION

RECOMMENDED FOR FURTHER BENEFIT STUDY

General considerations used in making this recommendation include:

- Patient population size
- Expected magnitude of individual benefits
- Data availability
- Ability to specify a model of the disease and its treatment.

The results of this and previous studies have shown that it is possible to specify the models and data for a broad range of candidate substances. The concept of transition probability modeling appears to be applicable in each case, and standard analytical techniques can be used to estimate the economic (direct) and social (indirect) benefits of the improved treatments made possible by space bioprocessing. Clearly, the next logical step in this work is the assembly of the data, and the development and operation of these models to estimate the benefits.

In addition to the candidate substances and clinical applications shown on the opposite page, it is also recommended that work continue to further refine the benefit estimates for the three previously studied substances and applications; namely, lymphocyte subgroup separation (end stage renal disease), urokinase (pulmonary embolisms) and Beta cells (diabetes).[1,2]

[1] Preliminary Benefit Analysis of Biological Space Processing, ECON, Inc., September 1976.

[2] Benefit Evaluation of Space Processing of Biological Materials. Contract NAS-9-15378, Final Report (in preparation).

RECOMMENDED FOR FURTHER BENEFIT STUDY

WARRANT DATA COLLECTION AND BENEFIT STUDY

- STEM CELLS FOR TRANSPLANT OF IMMUNE SYSTEM AS PRELUDE TO ORGAN TRANSPLANT
- MEGAKARYOCYTES FOR TRANSFUSION IN COMBINATION WITH CHEMOTHERAPY AND/OR IRRADIATION IN TREATMENT OF TUMOR CANCERS
- GRANULOCYTES FOR TRANSPLANT IN COMBINATION WITH CHEMOTHERAPY AND/OR IRRADIATION IN TREATMENT OF ACUTE MYELOBLASTIC LEUKEMIA
- PLASMA CELLS FOR TRANSPLANT IN PATIENTS WITH ACQUIRED HYPOAGAMMAGLOBULINEMIA
- PEPTIDE HORMONES; ACTH, FOR USE IN POST STEROID THERAPY
- LYMPHOCYTES, FOR TRANSFUSION IN PATIENTS WITH RHEUMATOID ARTHRITIS